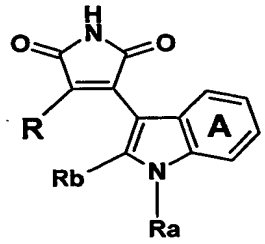
Claims:

1. Use of a an inhibitor of one or more of protein kinases PKC alpha, PKC beta, PKC gamma, PKC epsilon, PKC theta, CDK-1, KDR, PKA, Flt-1, Flt-2, Flt-3 and Flt-4, for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

2. The use according to claim 1 wherein the inhibitor is a compound of formula I



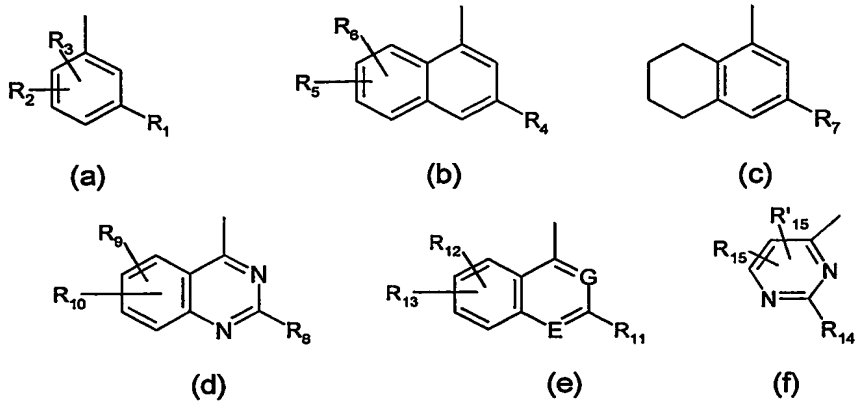
I

wherein

R_a is H; C_{1-4}alkyl; or C_{1-4}alkyl substituted by OH, NH_2, NHC_{1-4}alkyl or $N(di\text{-}C_{1-4}alkyl)_2$;

R_b is H; or C_{1-4}alkyl;

R is a radical of formula (a), (b), (c), (d), (e) or (f)



wherein

each of R_1, R_4, R_7, R_8, R_{11} and R_{14} is OH; SH; a heterocyclic residue; $NR_{16}R_{17}$ wherein each of R_{16} and R_{17}, independently, is H or C_{1-4}alkyl or R_{16} and R_{17} form together with the nitrogen atom to which they are bound a heterocyclic residue; or a radical of formula α

$$-X-R_c-Y \qquad (\alpha)$$

wherein X is a direct bond, O, S or NR_{18} wherein R_{18} is H or C_{1-4}alkyl,
R_c is C_{1-4}alkylene or C_{1-4}alkylene wherein one CH_2 is replaced by CR_xR_y wherein one of R_x and R_y is H and the other is CH_3, each of R_x and R_y is CH_3 or R_x and R_y form together $-CH_2-CH_2-$, and
Y is bound to the terminal carbon atom and is selected from OH, a heterocyclic residue and $-NR_{19}R_{20}$ wherein each of R_{19} and R_{20} independently is H, C_{3-6}cycloalkyl, C_{3-6}cycloalkyl-C_{1-4}alkyl, aryl-C_{1-4}alkyl or C_{1-4}alkyl optionally substituted on the terminal carbon atom by OH, or R_{19} and R_{20} form together with the nitrogen atom to which they are bound a heterocyclic residue;

each of R_2, R_3, R_5, R_6, R_9, R_{10}, R_{12}, R_{13}, R_{15} and R'_{15}, independently, is H, halogen, C_{1-4}alkyl, CF_3, OH, SH, NH_2, C_{1-4}alkoxy, C_{1-4}alkylthio, NHC_{1-4}alkyl, $N(di\text{-}C_{1-4}alkyl)_2$ or CN;

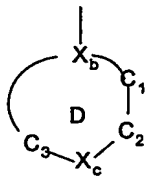
either E is –N= and G is –CH= or E is –CH= and G is –N=; and

ring A is optionally substituted,

or a salt thereof.

3. Use according to claim 1 or 2 wherein the inhibitor is a compound according to claim 2, wherein the heterocyclic residue as R_1, R_4, R_7, R_8, R_{11}, R_{14} or Y or formed, respectively, by $NR_{16}R_{17}$ or $NR_{19}R_{20}$, is a three to eight membered saturated, unsaturated or aromatic heterocyclic ring comprising 1 or 2 heteroatoms, and optionally substituted on one or more ring carbon atoms and/or on a ring nitrogen atom when present.

4. Use according to claim 1 or 2 wherein the inhibitor is a compound according to claim 2, wherein the heterocyclic residue as R_1, R_4, R_7, R_8, R_{11}, R_{14} or Y or formed, respectively, by $NR_{16}R_{17}$ or $NR_{19}R_{20}$, is a residue of formula (γ)



(γ)

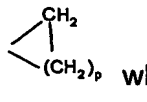
wherein

the ring D is a 5, 6 or 7 membered saturated, unsaturated or aromatic ring;

X_b is –N-, -C= or –CH-;

X_c is -N=, $-NR_f$-, $-CR_f'$= or $-CHR_f'$- wherein R_f is a substituent for a ring nitrogen atom and is selected from C_{1-6}alkyl; acyl; C_{3-6}cycloalkyl; C_{3-6}cycloalkyl-C_{1-4}alkyl; phenyl; phenyl-C_{1-4}alkyl; a heterocyclic residue; and a residue of formula β

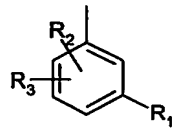
$$-R_{21}-Y' \qquad (\beta)$$

wherein R_{21} is C_{1-4}alkylene or C_{2-4}alkylene interrupted by O and Y' is OH, NH_2, $NH(C_{1-4}alkyl)$ or $N(C_{1-4}alkyl)_2$; and R_f' is a substituent for a ring carbon atom and is selected from C_{1-4}alkyl; C_{3-6}cycloalkyl optionally further substituted by C_{1-4}alkyl;  wherein p is 1, 2 or 3; CF_3; halogen; OH; NH_2; $-CH_2-NH_2$; $-CH_2-OH$; piperidin-1-yl; and pyrrolidinyl;
the bond between C_1 and C_2 is either saturated or unsaturated;
each of C_1 and C_2, independently, is a carbon atom which is optionally substituted by one or two substituents selected among those indicated above for a ring carbon atom; and
the line between C_3 and X_b and between C_1 and X_b, respectively, represents the number of carbon atoms as required to obtain a 5, 6 or 7 membered ring D.

5. use according to claim 1 to 4 wherein the inhibitor is a compound according to claim 2, wherein D is a piperazinyl ring optionally C- and/or N-substituted as specified in claim 4.

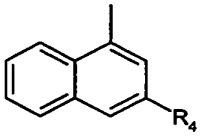
6. Use according to claim 1 or 2 wherein the inhibitor is a compound according to claim 2, wherein
Ra is H; CH_3; CH_2-CH_3; or isopropyl,
Rb is H; halogen; C_{1-6}alkoxy; or C_{1-6}alkyl, and either

I. R is a radical of formula (a)


(a)

wherein
R1 is piperazin-1-yl optionally substituted by CH_3 in position 3 or 4; or 4,7-diaza-spiro [2.5] oct-7-yl;
R_2 is Cl; Br; CF_3; or CH_3; and
R_3 is H; CH_3; or CF_3; R_3 being other than H when Ra is H or CH_3, Rb is H and R_1 is 4-methyl-1-piperazinyl; or

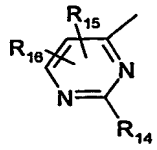
II. R is a radical of formula (b)


(b)

wherein

R_4 is piperazin-1-yl substituted in positions 3 and/or 4 by CH_3; or 4,7-diaza-spiro [2.5] oct-7-yl; Ra being other than H or CH_3 when R_4 is 4-methyl-1-piperazinyl; or

III. R is a residue of formula (c)



(c)

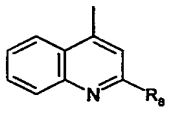
wherein

R_{14} is piperazin-1-yl optionally substituted by CH_3 in position 3 and/or 4 or in position 3 by ethyl, phenyl-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl or halogeno–C_{1-4}alkyl; or 4,7-diaza-spiro [2.5] oct-7-yl;

R_{15} is halogen; CF_3; or CH_3; R_{15} being other than CH_3 when Ra is H or CH_3, Rb is H and R_{14} is 4-methyl-1-piperazinyl; and

R_{16} is H; CH_3; or CF_3; R_{16} being other than H when R_{15} is Cl, Ra is H or CH_3, Rb is H and R_{14} is 4-methyl-1-piperazinyl; or

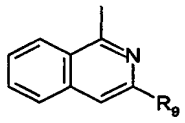
IV. R is a radical of formula (d)



(d)

wherein R_8 is piperazin-1-yl, 3-methyl-piperazin-1-yl or 4-benzyl-piperazin-1-yl; or

V. R is a radical of formula (e)



(e)

wherein R_9 is 4,7-diaza-spiro [2.5] oct-7-yl; or piperazin-1-yl substituted in position 3 by methyl or ethyl and optionally in position 4 by methyl;

or a pharmaceutically acceptable salt thereof.

7. Use according to claim 1 or 2 wherein the inhibitor is a compound according to claim 1, wherein

when R is of formula (a)

R_1 is -(4-methyl-piperazin-1-yl), 1-piperazinyl, 3-methyl-piperazin-1-yl or -(4,7-diaza-spiro[2.5]oct-7-yl)

R_2 is 2-Cl or 2-CH_3

R_3 is 3-CH_3, 3-CF_3or H

R_a is H or CH_3

And when,

R is of formula (b)

R_4 is -(4,7-diaza-spiro[2.5]oct-7-yl), 3-methyl-piperazin-1-yl or 4-methyl-3-methyl-piperazin-1-yl

R_a is H orCH_3

And when

R is of formula (c)

R_{14} is -4-methyl-piperazin-1-yl, 3-methyl-piperazin-1-yl, -4,7-diaza-spiro[2.5]oct-7-yl, 1-piperazinyl, 4-methyl-3-methyl-piperazin-yl, 3-methoxyethyl-piperazin-1-yl, 3-ethyl-piperazin-1-yl, 3-benzyl-piperazin-1-yl or 3-CH_2F-piperazin-1-yl

R_{15} is Cl, Br, CF_3, F

R_{16} is CH_3, H, CH_2-CH_3

R_a is H or CH_3

R_b is H, CH_2-CH_2-CH_3, F, $CH(CH_3)_2$, Cl, OCH_3, CH_3 or CH_2-CH_3

And when

R is of formula (d)

R_8 is 3-methyl-piperazin-1-yl, 4-benzyl-1-piperazinyl or 1-piperazinyl

R_a is CH_3 or H

And when

R is of formula (e)

R_9 is -4,7-diaza-spiro[2.5]oct-7-yl, 3-ethyl-piperazin-1-yl, 3-methyl-piperazin-1-yl, 4-methyl-3-methyl-piperazin-1-yl or 3-ethyl-piperazin-1-yl

R_a is H, CH_2-CH_3 or $CH(CH_3)_2$

R_b is CH_3, F, $CH(CH_3)_2$, OCH_3, CH_2-CH_3 or Cl

or a pharmaceutically acceptable salt thereof.

8. Use according to claim 1, 2 wherein the inhibitor is 3-[2-Chloro-5-(4-methyl-piperazin-1-yl)-3-trifluoromethyl-phenyl]-4-(1H-indol-3-yl)-pyrrole-2,5-dione or 3-(1H-Indol-3-yl)-4-[2-(4-methyl-piperazin-1-yl)-quinazolin-4-yl]-pyrrole-2,5-dione;

or a pharmaceutically acceptable salt thereof.

9. Use according to any one of the claims 1-8 wherein a daily dose of 10 to 800 mg of a compound is administered to an adult human.

10. Use according to any one of claims 1 – 8 wherein the disorder to be treated is selected from Down's Syndrome, memory and cognitive impairment, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, or cerebral hemorrhage with amyloidosis.

11. A method of treating mammals suffering from neurological and vascular disorders related to beta-amyloid generation and/or aggregation which comprises administering to a said mammal in need of such treatment a pharmaceutical composition comprising
(a) a dose, effective against neurological and vascular disorders related to beta-amyloid generation and/or aggregation, an inhibitor of formula I according to claim any one of the claims 1- 8 or a pharmaceutically acceptable salt thereof and
(b) a therapeutically effective amount of a second drug selected from drugs used to treat neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

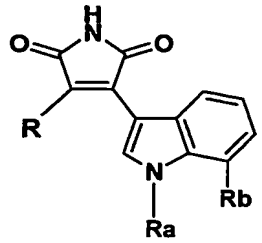
12. Use of an inhibitor according to any one of claims 1 - 8 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prevention of neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

13. A pharmaceutical composition for use in the treatment of a neurological and vascular disorders related to beta-amyloid generation and/or aggregation comprising an inhibitor of formula I according to claim any one of the claims 1- 8.

14. A method of treating a warm blooded animal having a neurological and vascular disorders related to beta-amyloid generation and/or aggregation comprising administering a therapeutically effective amount of an inhibitor according to any one of claims 1 – 8

15. A combination comprising an inhibitor according to any one of claims 1- 8, and a therapeutically effective amount of a second drug selected from drugs used to treat neurological and vascular disorders related to beta-amyloid generation and/or aggregation.

16. A commercial package comprising an inhibitor of formula I



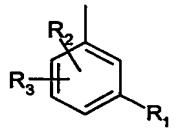
I

wherein

Ra is H; CH_3; CH_2-CH_3; or isopropyl,

Rb is H; halogen; C_{1-6}alkoxy; or C_{1-6}alkyl, and either

I. R is a radical of formula (a)



(a)

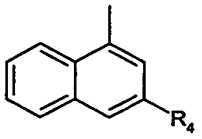
wherein

R1 is piperazin-1-yl optionally substituted by CH_3 in position 3 or 4; or 4,7-diaza-spiro [2.5] oct-7-yl;

R_2 is Cl; Br; CF_3; or CH_3; and

R_3 is H; CH_3; or CF_3; R_3 being other than H when Ra is H or CH_3, Rb is H and R_1 is 4-methyl-1-piperazinyl; or

II. R is a radical of formula (b)

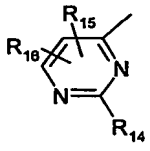


(b)

wherein

R_4 is piperazin-1-yl substituted in positions 3 and/or 4 by CH_3; or 4,7-diaza-spiro [2.5] oct-7-yl; Ra being other than H or CH_3 when R_4 is 4-methyl-1-piperazinyl; or

III. R is a residue of formula (c)



(c)

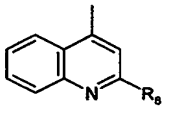
wherein

R_{14} is piperazin-1-yl optionally substituted by CH_3 in position 3 and/or 4 or in position 3 by ethyl, phenyl-C_{1-4}alkyl, C_{1-4}alkoxy-C1-4alkyl or halogeno–C_{1-4}alkyl; or 4,7-diaza-spiro [2.5] oct-7-yl;

R_{15} is halogen; CF_3; or CH_3; R_{15} being other than CH_3 when Ra is H or CH_3, Rb is H and R_{14} is 4-methyl-1-piperazinyl; and

R_{16} is H; CH_3; or CF_3; R_{16} being other than H when R_{15} is Cl, Ra is H or CH_3, Rb is H and R_{14} is 4-methyl-1-piperazinyl; or

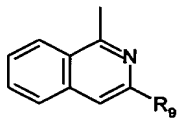
IV. R is a radical of formula (d)



(d)

wherein R_8 is piperazin-1-yl, 3-methyl-piperazin-1-yl or 4-benzyl-piperazin-1-yl; or

V. R is a radical of formula (e)



(e)

wherein R_9 is 4,7-diaza-spiro [2.5] oct-7-yl; or piperazin-1-yl substituted in position 3 by methyl or ethyl and optionally in position 4 by methyl;

or a pharmaceutically acceptable salt thereof in the treatment of neurological and vascular disorders related to beta-amyloid generation and/or aggregation,

together with instructions for simultaneous, separate or sequential use thereof in the treatment of a proliferative disease.